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Article

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Periselectivity in the aza-Diels–Alder cycloaddition between α-oxoketenes and *N*-(5-pyrazolyl)imines: a combined experimental and theoretical study

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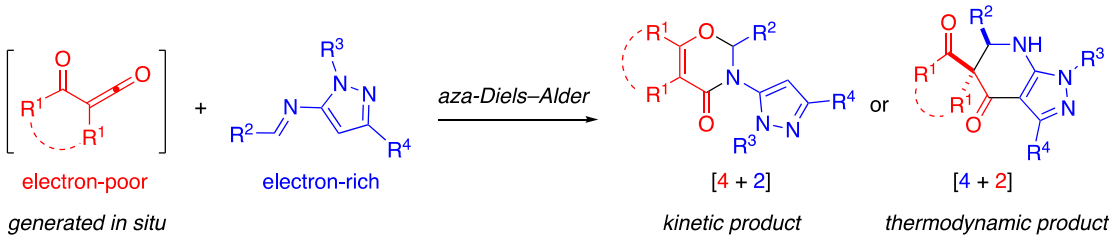
GRAPHICAL ABSTRACT

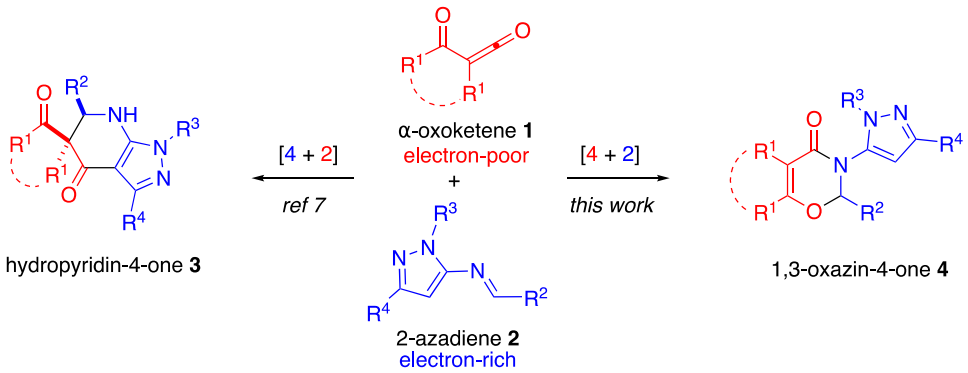


ABSTRACT

The thermal 6π aza-Diels–Alder cycloadditions between α-oxoketenes, *in situ* derived from a thermally induced Wolff rearrangement of 2-diazo-1,3-diketones, and *N*-(5-pyrazolyl)imines as prototypical electron-rich 2-azadienes lead to two distinct sets of products, essentially as a function of the nature of the α-oxoketenes involved. For instance, cyclic five-membered α-oxoketenes lead preferentially to spiro hydropyridin-4-ones, which involves the α-oxoketenes as the 2π partners at their C=C double bond and the *N*-(5-pyrazolyl)imines as the 4π partners at their 2-azadiene moiety. In contrast, other cyclic and acyclic α-oxoketenes lead preferentially to 1,3-oxazin-4-ones, which now involves the α-oxoketenes as the 4π partners at their 1-oxadiene moiety and the *N*-(5-pyrazolyl)imines as the 2π partners at their C=N double bond. A computational modeling study using DFT methods allowed rationalizing this change of periselectivity: the formation of spiro hydropyridin-4-ones is under thermodynamic control while the formation of 1,3-oxazin-4-ones is kinetically controlled, and slightly thermodynamically disfavored in the five-membered ring series. The competing cyclodimerization of the α-oxoketenes is also studied in detail.

INTRODUCTION

α-Oxoketenes are short-lived chemical species with a long history,[1] and with few exceptions, they cannot be isolated and must be generated *in situ*.[2] They are routinely obtained either from the thermal decomposition of dioxinones with concomitant extrusion of acetone,[3] or from the thermal or photochemical Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds extruding nitrogen gas.[1,4] α-Oxoketenes are electrophilic species with widespread applications in organic synthesis, from the preparation of simple β-oxocarbonyl derivatives[5a] to the total synthesis of natural products[2d,e] and complex heterocycles.[5b] As to their annulation and cycloaddition reactions, they most commonly react with unsaturated substrates as 4π partners, *i.e.* 1-oxadienes, in inverse electron-demand formal Diels-Alder processes.[2] However, in a few occasions, α-oxoketenes were found to react preferentially as 2π partners in normal electron-demand formal aza-Diels–Alder and 1,3-dipolar cycloadditions with 4π electron-rich substrates including 1-azadienes,[6] 2-azadienes,[7] and azomethine imines.[8] For instance, we previously reported that electron-rich 2-azadienes such as *N*-hetaryl imines **2** generated from 5-amino-pyrazoles could react with five-membered cyclic α-oxoketenes as a chemo-, regio- and diastereoselective entry to spiro hydropyridin-4-ones of type **3** (Scheme 1, left).[7] More recently, re-examination of this reaction with larger cyclic and acyclic α-oxoketenes has unexpectedly led to the formation of 1,3-oxazin-4-ones of type **4** instead of the awaited hydropyridin-4-one products **3** (Scheme 1, right). The reasons responsible for this change of periselectivity, the selectivity in formation of the pericyclic products,[9] within a relatively homogeneous class of substrates have been identified by a combination of experimental and computational studies as detailed hereafter.



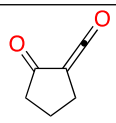
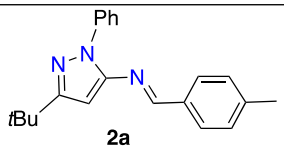
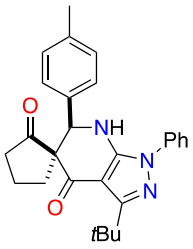
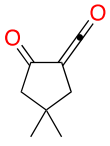
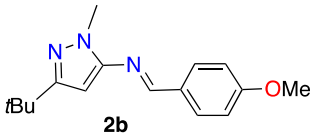
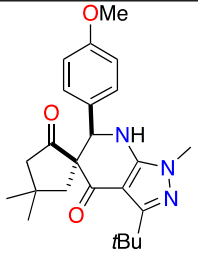
Scheme 1. Periselectivity in the formal aza-Diels–Alder cycloadditions of α-oxoketenes with 2-azadienes derived from 5-aminopyrazoles.

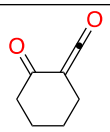
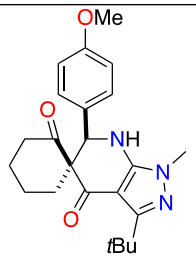
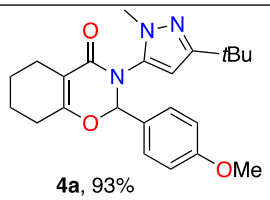
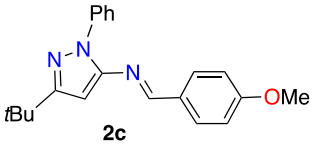
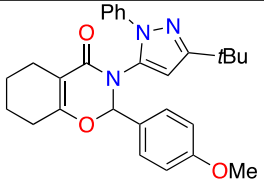
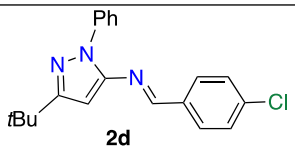
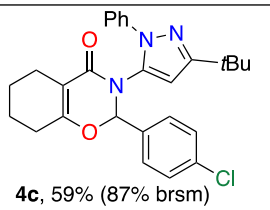
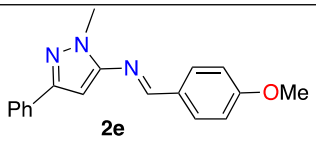
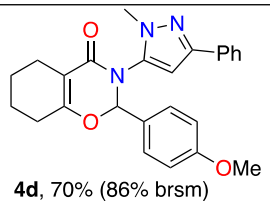
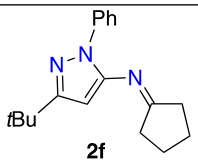
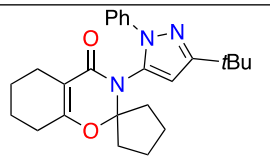
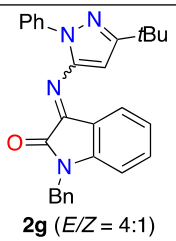
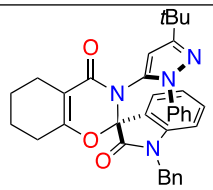
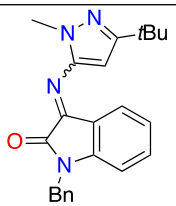
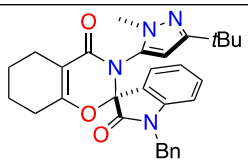
RESULTS AND DISCUSSION

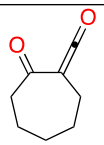
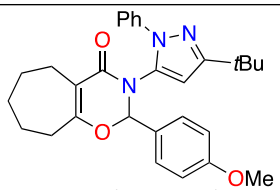
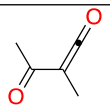
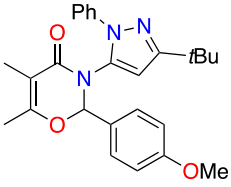
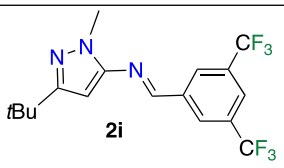
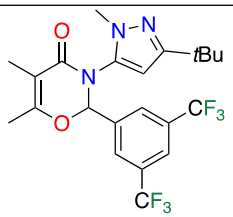
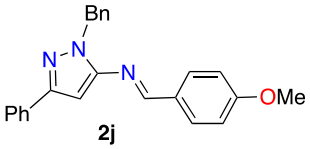
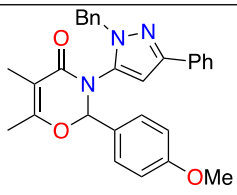
The new experimental observations are summarized in Table 1 (entries 4–14), together with a few results from our previous study[7] for the sake of comparison (entries 1–3). It was previously found that the five-membered cyclic α-oxoketene **1a** derived from 2-diazo-1,3-cyclohexanedione reacted with the *N*-(5-pyrazolyl)aldimine **2a** to give diastereoselectively the spiro hydropyridin-4-one **3a** product after 4 min at 150 °C (entry 1). A similar reaction with the five-membered cyclic α-oxoketene **1b** derived from diazodimedone and aldimine **2b** gave the spiro hydropyridin-4-one **3b** in comparable yield and stereoselectivity after 4 min at 180 °C (entry 2), and the six-membered cyclic α-oxoketene **1c** derived from 2-diazo-1,3-cycloheptanedione reacted with the same aldimine **2b** to give the corresponding spiro

hydropyridin-4-one **3c**, albeit in reduced yield and after 45 min at 250 °C (entry 3). In contrast, we observed more recently that the reactions between the six-membered cyclic α-oxoketene **1c** and aldimines **2b–e** afforded the corresponding 1,3-oxazin-4-ones **4a–d**, respectively, in good yields (entries 4–7). Complementarily, α-oxoketene **1c** reacted with ketimine **2f** derived from cyclopentanone to afford the spiro oxazinone **4e** in good yield (entry 8), and with the ketimines **2g** and **2h** obtained from *N*-benzyl isatin to give the spirooxindoles **4f** and **4g** also in good yields (entries 9 and 10). Interestingly, in the latter two cases, the products were obtained as mixtures of two rotamers in a 1.6:1 ratio at 25 °C due to the presence of both a stereogenic center at the spiro carbon atom and a stereogenic axis along the C–N bond linking the pyrazolyl substituent to the oxazinone core.[10] The free Gibbs energies of the optimized conformations of both rotamers **4f** and **4g** were computed (see details in the Supporting Information), which showed a slight preference for the *(aS,R)*-configured rotamer for **4f** [$\Delta(\Delta G)$ = -4.3 kJ.mol^{-1}] and for the *(aR,R)*-configured rotamer for **4g** [$\Delta(\Delta G)$ = -5.8 kJ.mol^{-1}] at 25 °C. The barriers to epimerization along the C–N stereogenic axes were computed at 91.7 and 82.9 kJ.mol^{-1}, respectively, corresponding to half-lives in the magnitude of seconds to minutes at 25 °C in agreement with the experimental observations. The reaction of the seven-membered cyclic α-oxoketene **1d** with aldimine **2c** afforded the 1,3-oxazin-4-one **4h** in 36% isolated yield (entry 11). Finally, a series of reactions with the acyclic α-oxoketene **1e** derived from the Wolff rearrangement of 2-diazoacetylacetone combined with the *N*-(5-pyrazolyl)aldimines **2c**, **2i** and **2j** afforded the 1,3-oxazin-4-ones **4i**, **4j** and **4k** in 64%, 49% and 62% yield, respectively (entries 12–14). The reaction between the α-oxoketene derived from methyl 2-diazoacetylacetate (involving the migration of the methyl group during the Wolff rearrangement) and imine **2a** afforded a complex mixture of unidentified products.

Table 1. Reactions of α-oxoketenes with *N*-(5-pyrazolyl)imines[a]

entry	α-oxoketene	*N*-(5-pyrazolyl)imine	conditions	cycloadduct
1[b]	 **1a**	 **2a**	2 × (1.2 equiv 2-diazo-1,3-cyclohexanedione, 150 °C, 2 min)	 *rac-(R,R)*-**3a**, dr > 25:1, 72%
2[b]	 **1b**	 **2b**	2 × (1.2 equiv diazodimedone, 180 °C, 2 min)	 *rac-(R,R)*-**3b**, dr > 25:1, 81%

3[b]	 **1c**	**2b**	3 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 250 °C, 15 min)	 *rac-(R,R)*-**3c**, dr > 25:1, 30%
4	**1c**	**2b**	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 **4a**, 93%
5	**1c**	 **2c**	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 **4b**, 80% (95% brsm)
6	**1c**	 **2d**	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 **4c**, 59% (87% brsm)
7	**1c**	 **2e**	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 180 °C, 2 min)	 **4d**, 70% (86% brsm)
8	**1c**	 **2f**	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 **4e**, 80%
9[c]	**1c**	 **2g** (*E*/*Z* = 4:1)	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 *rac-(aS,R)*-**4f**, dr = 1.6:1, 83%
10[c]	**1c**	 **2h** (*E*/*Z* = 4:1)	2 × (1.2 equiv 2-diazo-1,3-cycloheptanedione, 150 °C, 2 min)	 *rac-(aR,R)*-**4g**, dr = 1.6:1, 77%

11	 **1d**	**2c**	2 × (1.2 equiv 2-diazo-1,3-cyclooctanedione, 150 °C, 2 min)	 **4h**, 36% (65% brsm)
12	 **1e**	**2c**	2 × (1.2 equiv 2-diazo-acetylacetone, 180 °C, 2 min)	 **4i**, 64% (91% brsm)
13	**1e**	 **2i**	2 × (1.2 equiv 2-diazo-acetylacetone, 180 °C, 2 min)	 **4j**, 49% (98% brsm)
14	**1e**	 **2j**	2 × (1.2 equiv 2-diazo-acetylacetone, 180 °C, 2 min)	 **4k**, 62% (85% brsm)

a. All reactions in toluene (ca. 0.1 M) in sealed reaction vessels under microwave irradiation with two heating/cooling cycles. Periselectivity ≥ 20:1 in all cases. brsm = based on recovered starting material **2**.
b. Previously reported results from reference 7 included for direct comparison.
c. dr at 25 °C.

From the results in Table 1, it can be noted: i) that five-membered cyclic α-oxoketenes led exclusively to spiro hydropyridin-4-one of type **3**; ii) that other cyclic or acyclic α-oxoketenes led very preferentially to 1,3-oxazin-4-ones of type **4** pointing out the importance of the ring size in these reactions; iii) that a thermodynamic *versus* kinetic control of the reaction is seemingly operative in the reactions between the six-membered α-oxoketene **1c** and *N*-(5-pyrazolyl)aldimine **2b** (compare entries 3 and 4); and iv) that some unreacted aldimine substrate could be recovered in many cases after the reaction despite the use of excess α-oxoketene diazo precursor (2 × 1.2 equiv, 2.4 equiv in total). With the intention to rationalize these experimental observations, the formal aza-Diels–Alder cycloaddition between the α-oxoketenes **1a**, **1c** or **1e** and the model *N*-(5-pyrazolyl)aldimine **2k** were analyzed by computational DFT methods. Because subtle differences were anticipated, the calculations were performed using B3LYP-D3/6-311++G(d,p), a relatively robust level of theory that includes polarization and diffuse functions on all atoms and the Grimme's D3 London dispersion correction, with the iefpcm solvation model for toluene (see details in the Supporting Information). The reactions of the five-membered α-oxoketene **1a** with the model aldimine **2k** were first considered. Paralleling our early investigations,[7] it was found that the diastereoselective formation of the model spiro hydropyridin-4-one **3d** is exergonic [Δ(ΔG) = -48.2 kJ.mol^{-1}] and results from a Friedel–Crafts/Mannich sequence operating in three steps through intermediates **Int1** (fleeting) and **Int2** as depicted in Figure 1a with an overall activation barrier computed at +78.1 kJ.mol^{-1}. The conversion of intermediate **Int2** into

product **3d** is a concerted asynchronous proton transfer/*6-enol-exo–endo-trig* cyclization that controls the relative stereochemistry in the product. Examination of the concurrent reaction leading to the model 1,3-oxazin-4-one **4l** revealed a slightly endergonic [$\Delta(\Delta G)$ = +6.7 kJ.mol^{-1}] concerted very asynchronous process, formation of the N–C bond being largely in advance of the formation of the O–C bond, with a barrier computed at +71.2 kJ.mol^{-1} (Figure 1b).[11] In line with the experimental observations, this shows that the formation of the spiro hydropyridin-4-one **3d** is thermodynamically favored over the formation of the 1,3-oxazin-4-one **4l**, whatever the reaction temperature and time. The requirement for excess α-oxoketenes **1a,b** in their aza-Diels–Alder reaction with aldimines of type **2** indicates that some competing process consumes the α-oxoketenes under the optimized reaction conditions. Some α-oxoketenes have previously been shown to cyclodimerize through [4 + 2] cycloadditions[2,12] as illustrated in Figure 1c with the computed cyclodimerization energy profile of α-oxoketene **1a** into cyclodimer **5a**. However, alternative cyclodimerization processes are possible.[13] The formation of the cyclodimer **5a** was computed as a concerted asynchronous exergonic process [$\Delta(\Delta G)$ = -47.7 kJ.mol^{-1}] requiring only +72.7 kJ.mol^{-1} of activation energy (Figure 1c), and it is thus in competition with the formation of the spiro hydropyridin-4-one **3d**. Experimentally, the dimer **5a** could indeed be detected in the crude reaction mixture leading to **3a** as a minor byproduct while the major byproduct was the rearranged dimer **6a** (**6a**/**5a** $\approx$ 2:1 as determined by NMR analyses). The formation of **6a** can be explained by a thermodynamically favored [$\Delta(\Delta G)$ = -7.1 kJ.mol^{-1}] Lewis base-catalyzed ring rearrangement of **5a** via the zwitterionic intermediate **Int3** as depicted in Figure 1c,[7,14] with the Lewis base catalyst being in this case the imine **2a** and/or the product **3a** itself. In control experiments, the dielectric heating of a toluene solution of 2-diazo-1,3-cyclohexanedione at 160 °C for 5 min produced the dimer **5a** quantitatively (Scheme 2), while the same reaction conducted in the presence of *N*,*N*-dimethylallyl amine as the Lewis base promoter, afforded essentially the rearranged dimer **6a**, the structure of which could be confirmed by single-crystal X-ray diffraction analysis.[15] Interestingly, the structure of the rearranged cyclodimer **6a** was initially proposed in 1963 as the product of the reaction of adipyl dichloride with triethylamine, and its formation postulated to occur through the intermediate α-oxoketene **5a**[11] and a subsequent rearrangement, a spectacular cascade reaction not rationalized at the time.[16] The present work offers a satisfactory explanation for these early observations on the dimerization of five-membered cyclic α-oxoketenes, and for their preferred periselectivity as 2π partners in normal electron-demand formal aza-Diels–Alder processes involving *N*-hetaryl imines as 2-azadienes.

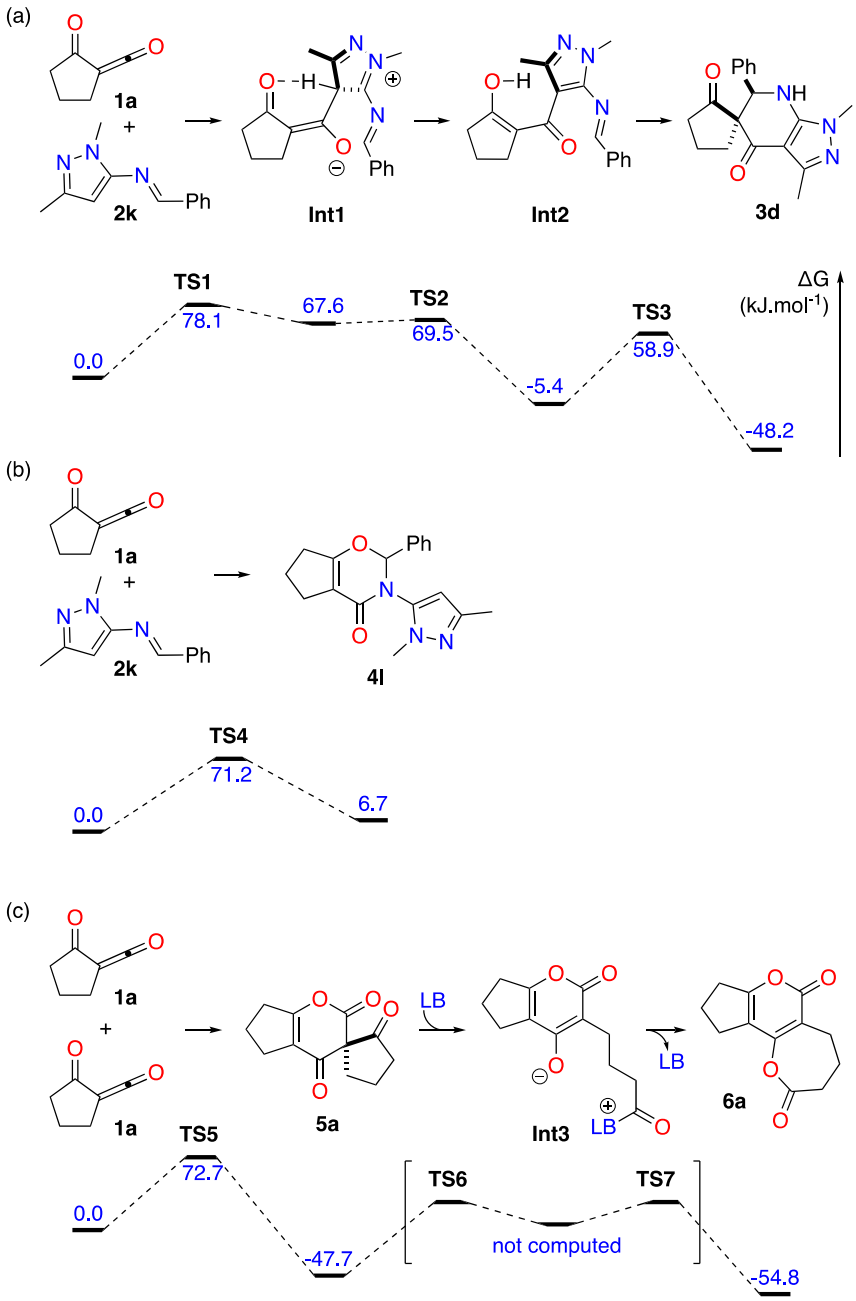
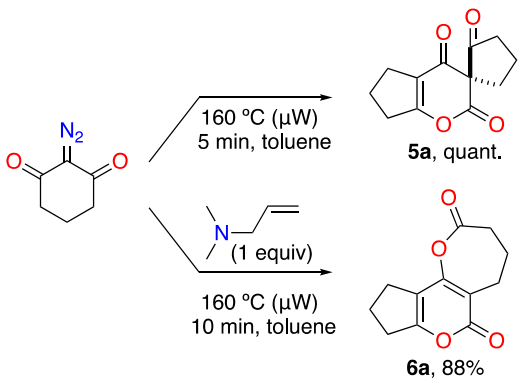


Figure 1. Free Gibbs energy profiles computed at 298 K [DFT, B3LYP-D3/6-311++G(d,p)] of some Diels–Alder reactions involving α-oxoketene **1a**. (a) Model reaction between α-oxoketene **1a** and aldimine **2k** leading to spiro hydropyridin-4-one **3d**. (b) Model reaction between α-oxoketene **1a** and aldimine **2k** leading to 1,3-oxazin-4-one **4l**. (c) Cyclodimerization of α-oxoketene **1a** leading to dimer **5a** and its rearranged product **6a**; LB = Lewis base.



Scheme 2. Control experiments for the synthesis of dimer **5a** and its Lewis base-catalyzed rearranged product **6a**.

The results of the DFT calculations in the six-membered ring series are summarized in Figure 2. Modeling the aza-Diels–Alder reaction between the six-membered cyclic α-oxoketene **1c** and the aldimine **2k** showed that the model spiro hydropyridin-4-one **3e** is the thermodynamic product with $\Delta(\Delta G)$ = -20.6 kJ.mol^{-1}, and that the model 1,3-oxazinone product **4m** is the kinetic product with $\Delta(\Delta G^{\neq})$ = -10.2 kJ.mol^{-1} (Figure 2a,b). The major difference between the five- and six-membered ring series resides in the relative stability of the 1,3-oxazin-4-one products: in the five-membered ring series, the formation of **4l** is slightly endergonic as shown in Figure 1b, while in the six-membered ring series the formation of **4m** is exergonic. This difference was attributed to the greater ring strain induced by the double bond at the ring junction in the five-membered ring series. Complementarily, the plausible formation of cyclodimer **5c** from α-oxoketene **1c**[12a] was computed with a barrier at 87.5 kJ.mol^{-1} and a stabilization energy of -61.2 kJ.mol^{-1}, and the Lewis base-catalyzed rearrangement of cyclodimer **5c** involving the formation of an eight-membered ring in **6c** was unsurprisingly found thermodynamically disfavored, though by only a few kJ.mol^{-1} (Figure 2c). It was concluded that six-membered cyclic α-oxoketenes preferentially react as 4π partners, i.e. 1-oxadienes, in inverse electron-demand formal aza-Diels-Alder processes in their reactions with *N*-hetaryl imines to afford 1,3-oxazin-4-ones of type **4** for kinetic reasons. The calculations also indicated that this reaction is in competition with the cyclodimerization of the α-oxoketene, justifying for the introduction of the diazo precursor in excess. However, providing that enough energy is brought to the reaction mixture to allow for the retro-cyclodimerization of **5c** at a significant rate ($t_{1/2} \approx 46$ s at 250 °C for an activation energy of 148.7 kJ.mol^{-1}, see **5c** → **1c** in Figure 2c), thermodynamic control becomes operative resulting in a switch of periselectivity in this series allowing for the formation of a spiro hydropyridin-4-one of type **3** (see entry 3, Table 1).

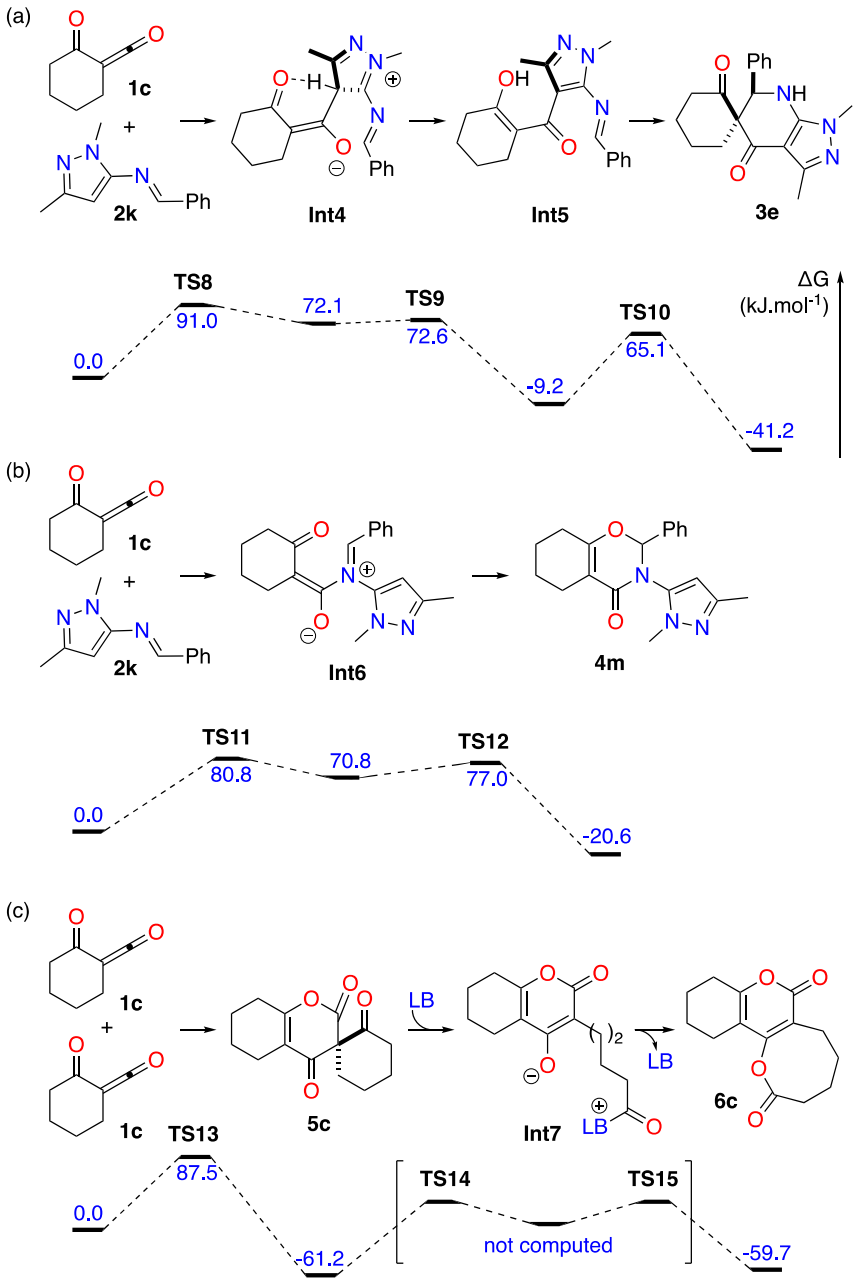


Figure 2. Free Gibbs energy profiles computed at 298 K [DFT, B3LYP-D3/6-311++G(d,p)] of some Diels–Alder reactions with α-oxoketene **1c**. (a) Model reaction between α-oxoketene **1c** and aldimine **2k** leading to spiro hydropyridin-4-one **3e**. (b) Model reaction between α-oxoketene **1c** and aldimine **2k** leading to 1,3-oxazin-4-one **4m**. (c) Plausible cyclodimerization of α-oxoketene **1c** leading to dimer **5c** and its rearranged product **6c**; LB = Lewis base.

The situation is more complex for the reactions with the acyclic α-oxoketene **1e** because of the co-existence of both conformers *s-cis*-**1e** and *s-trans*-**1e** in a ca. 1:20 ratio at 180 °C according to the computational model [$\Delta(\Delta G)$ = 11.3 kJ.mol^{-1}, $\Delta G^{\neq}$ = 53.9 kJ.mol^{-1}] illustrated in Figure 3. Paralleling the previous calculations, formation of the model hydropyridin-4-one **3f** was found under thermodynamic control [$\Delta(\Delta G)$ = -26.8 kJ.mol^{-1}, Figure 3a,b]. Notably, the calculations indicated that only the *s-cis* conformer of α-oxoketene **1e** is amenable to the Friedel–Crafts acylation, highlighting the crucial assistance of the ketone

carbonyl group of the α-oxoketene in the Friedel–Crafts desaromatization/rearomatization process.[17] Conversely, the model 1,3-oxazin-4-one **4n** was computed as the kinetic product with $\Delta(\Delta G^{\neq})$ = -10.8 kJ.mol^{-1} (Figure 3a,b). This is in good agreement with the experimental results that have shown the preferential formation of the 1,3-oxazin-4-ones **4i-k** after short reaction times at 180 °C (Table 1, entries 12–14). Some plausible [2+2] cycloadditions between α-oxoketene *s-trans*-**1e** and the model aldimine **2k** leading to the corresponding β-lactams were also investigated computationally and found largely kinetically disfavored when compared to the aza-Diels–Alder processes discussed herein (see the Supporting Information). As above, significant amounts of unreacted aldimines were recovered after the reactions, indicating some competing dimerization of the acyclic α-oxoketene **1e**.[12c] Computational modeling of the plausible reaction paths leading to the cyclodimer **5e** from *s-cis*-**1e** and *s-trans*-**1e** led to the identification of two distinct processes with nearly identical activation barriers (Figure 3c): i) the direct concerted asynchronous [4+2] cycloaddition between the 1-oxadiene in *s-cis*-**1e** and the ketene double bond in *s-trans*-**1e** with a barrier computed at 115.3 kJ.mol^{-1}, and ii) a two-step process with a barrier computed at 115.2 kJ.mol^{-1} initiated by the concerted asynchronous [4+2] cycloaddition between the 1-oxadiene in *s-cis*-**1e** and the ketone carbonyl group in *s-trans*-**1e** to give the ketene intermediate **7e**,[13] the Cope-like rearrangement of which can provide the cyclodimer **5e** via **TS23**. Alternative [4+2], [2+2] and [4+4] cyclodimerization processes of *s-cis*-**1e** and/or *s-trans*-**1e** were also computed and found kinetically and/or thermodynamically disfavored (see the Supporting Information). In a control experiment, heating a toluene solution of 2-diazoacetylacetone with microwaves at 180 °C for 2 minutes afforded a somehow complex mixture of products (Scheme 3), which contrasts with the very clean α-oxoketene cyclodimerization observed for the reaction of 2-diazo-1,3-cyclohexanedione (Scheme 2). The structure of the major component of this mixture was tentatively attributed to the cyclodimer **5e** by ^{1}H NMR analysis of the crude reaction mixture because we failed at isolating this product by silica gel chromatography or crystallization. Instead, crystallization from the crude mixture (slow evaporation of the solvent) allowed the isolation of the 4-hydroxy-*2H*-pyran-2-one **8e** (ca. 30%), the structure of which was ascertained by X-ray diffraction analysis.[15] It can reasonably be surmised that cyclodimer **5e** is the actual major product of the cyclodimerization of α-oxoketene **1e**, and that in the presence of atmospheric water it can hydrolyze into the deacetylated product **8e**, a known pyran-2-one previously employed for applications in the total syntheses of naturally occurring pyrones.[18]

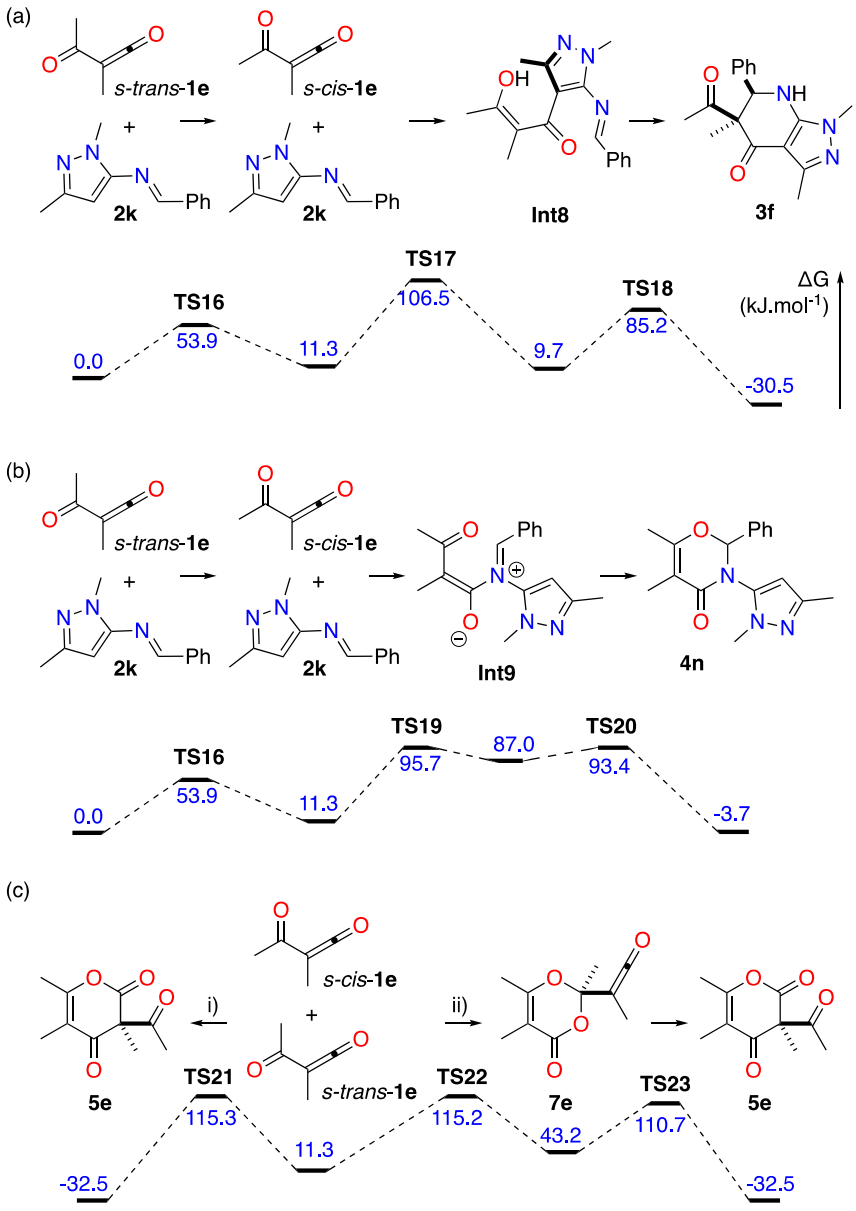
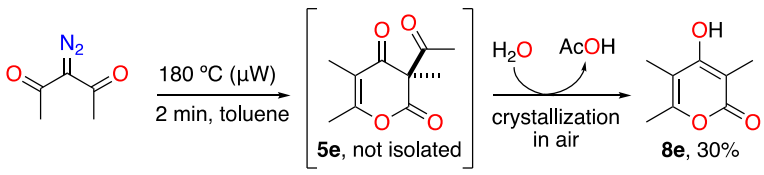


Figure 3. Free Gibbs energy profiles computed at 298 K [DFT, B3LYP-D3/6-311++G(d,p)] of some Diels–Alder reactions with α-oxoketene **1e**. (a) Model reaction between α-oxoketene **1e** and aldimine **2k** leading to hydropyridin-4-one **3f**. (b) Model reaction between α-oxoketene **1e** and aldimine **2k** leading to 1,3-oxazin-4-one **4n**. (c) Plausible cyclodimerization processes of α-oxoketene **1e** leading to dimer **5e**.



Scheme 3. Control experiments on the cyclodimerization of α-oxoketene **1e**.

For all model reactions above, the computed activation barriers at 298 K correspond to significant reaction rates at temperatures below 150 °C, and the same holds for calculations at 150 °C (see the Supporting Information). Thus, it is very likely that some chemistry is still going on during the experimental cooling cycles, blurring the image. Examination of the frontier orbitals in the α-oxoketenes **1a**, **1c** and *cis*-**1e** revealed that their LUMO are essentially located over the two atoms of the ketene C=O bonds with the π* system parallel to the mean plane of the molecule (Figure 4). In contrast, their LUMO+1 are principally distributed over the ketene C=C bonds and ketone C=O bonds with the π* system now perpendicular to the mean plane of the molecule. Thus, in all their reactions with the model 2-azadiene **2k**, the transformations are initiated by an overlap between the HOMO of **2k** (through its 4-C or 2-N atom depending on the periselectivity) and the LUMO of the α-oxoketenes located in the mean plane of the molecules, not perpendicular to it as in standard Diels–Alder cycloadditions. More generally, the localization of the LUMO of the α-oxoketenes on their ketene carbonyl groups accounts for the stepwise or highly asynchronous nature of the [4 + 2] processes described herein.

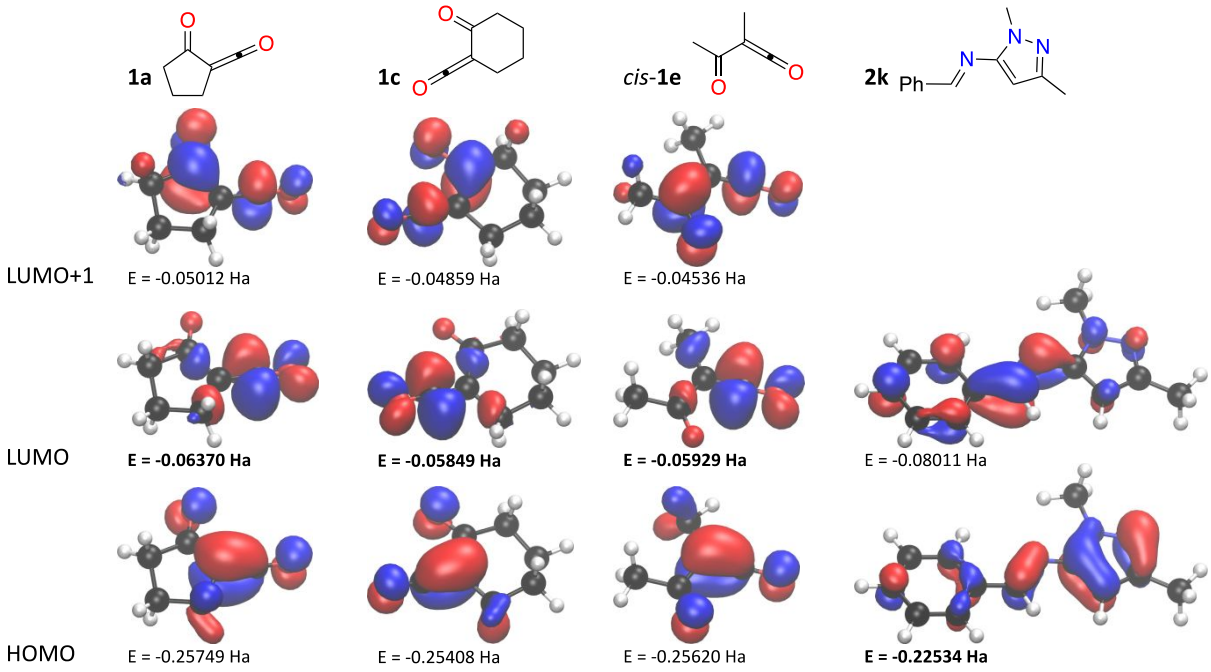


Figure 4. Contour plots and energies of the frontier orbitals in the α-oxoketenes **1a**, **1c** and *cis*-**1e**, and the model 2-azadiene **2k**.

CONCLUSIONS

The reactions between α-oxoketenes generated by a thermally induced Wolff rearrangement of 2-diazo-1,3-diketones and some *N*-(5-pyrazolyl)imines were studied in detail. Among the many possibilities of formal or true cycloadditions in principle allowed with these poly-unsaturated substrates, two 6π formal aza-Diels–Alder cycloadditions were observed experimentally: cyclic five-membered α-oxoketenes were found to react preferentially as 2π partners through their C=C double bond with *N*-hetaryl imines reacting as 4π 2-azadienes to produce spiro hydropyridin-4-ones of type **3**, while other cyclic or acyclic α-oxoketenes

predominantly reacted as 4π partners, i.e. 1-oxadienes, with the C=N bond of the *N*-hetaryl imines as the 2π partners to produce 1,3-oxazin-4-ones of type **4**. Both reactions are synthetically relevant to the preparation of chiral *N*-heterocycles and alkaloids, which called for a rational of the observed periselectivity in these formal aza-Diels–Alder cycloadditions. A computational modeling study using DFT allowed understanding the fundamental reasons at the origin of the observed change in periselectivity. It was generally found that the formation of spiro hydropyridin-4-ones of type **3** is under thermodynamic control while 1,3-oxazin-4-ones of type **4** are produced under kinetic control. However, it does not seem practical to control efficiently the reactions outcomes by adjusting their temperature and time. One reason for this is the existence of competing decomposition pathways of the α-oxoketenes, for instance, the formation of cyclodimers of type **5** and/or their rearranged derivatives of type **6**. These findings are expected to have a significant impact on the development of applications of α-oxoketenes in organic synthesis.

EXPERIMENTAL SECTION

General Information: All reagents were purchased from commercial sources and used without further purification unless otherwise noted. All compounds were weighed and handled in air at room temperature. Microwave-assisted heating was performed using a professional Anton-Paar Monowave 300 system in specific sealed tubular reaction vessels. The reactions were monitored by TLC (60 F_{254}) visualized by UV lamp (254 nm or 365 nm). Flash chromatography was performed on silica gel (particle size 40−63 μm). Petroleum ether refers to the fraction with bp = 40–60 °C. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) at 298 K in $CDCl_3$ using as internal standards the residual non-deuterated signal for ^{1}H NMR (δ = 7.26 ppm) and the deuterated solvent signal for ^{13}C NMR spectroscopy (δ = 77.16 ppm). DEPT-135 experiments were used to determine the multiplicity of the ^{13}C resonances. Chemical shifts (δ) are given in ppm, coupling constants (*J*) are given in Hz, and the classical abbreviations are used to describe the multiplicity of the ^{1}H resonances. High-resolution mass spectra were recorded in triplicate at the Spectropole (https://fr-chimie.univ-amu.fr/spectropole/). 2-Diazo-1,3-diketones,[19] aldimines **2a–e** and **2i**,[7] and ketimines **2f–h**[20] were prepared as previously reported in similar yields and purity.

Aldimine 2j: A 10 mL sealable (with screw cap) tubular reaction vessel containing a Teflon-coated magnetic stirring bar was charged with 1-benzyl-3-phenyl-*1H*-pyrazol-5-amine (270 mg, 1.08 mmol), *p*-anisaldehyde (160 mg, 1.18 mmol), 2 pellets of solid KOH and 4.0 mL of anhydrous toluene. The reaction vessel was sealed, and the mixture was heated at 90 °C for 5 hours with stirring, cooled down to room temperature and filtered over celite. The filtrate was concentrated under vacuum and the resulting solid material was triturated with petroleum ether/ethyl acetate 9:1 to afford, after filtration and drying in vacuo, aldimine **2j** (380 mg, 95%) as a pale yellow solid. **Rf** (EtOAc/petroleum ether 1:10) = 0.45. **Mp** = 62 °C (amorphous). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 162.7, 159.0, 150.9, 150.6, 137.8, 133.8, 130.7, 128.9, 128.5, 128.5, 127.7, 127.6, 127.4, 125.5, 114.3, 114.3, 88.5, 55.4, 51.6. **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 8.60 (s, 1H), 7.92–7.80 (m, 4H), 7.43–7.23 (m, 8H), 7.04–6.96 (m, 2H), 6.54 (s, 1H), 5.58 (s, 2H), 3.88 (s, 3H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{22}N_3O^+$ 368.1757; Found 368.1757.

General procedure for the aza-Diels–Alder reactions (Table 1, entries 4–14). A solution of the *N*-hetaryl imine **2** (ca. 0.2 mmol) and the corresponding 2-diazo-1,3-dicarbonyl precursor of

the α-oxoketene **1** (1.2 equiv) in 2.0 mL anhydrous toluene placed in a 10 mL sealed tube containing a Teflon-coated magnetic stirring bar was irradiated with microwaves at 150 or 180 °C for 2 minutes and cooled down to 55 °C by an air flow over 5–6 minutes. A second portion of the 2-diazo-1,3-dicarbonyl compound (1.2 equiv) was added to the reaction mixture that was irradiated at the same temperature for 2 additional minutes, cooled down to 55 °C by an air flow over 5–6 minutes, concentrated, analyzed by ^{1}H NMR and purified by flash chromatography on silica gel to afford product **4**.

1,3-Oxazin-4-one 4a. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 40.5 mg, 0.53 mmol) and aldimine **2b** (60 mg, 0.22 mmol) in 2.0 mL of anhydrous toluene, compound **4a** was obtained as a white solid (81 mg, 93%). **Rf** (EtOAc/ petroleum ether 1:3) = 0.11. **Mp** = 109–110 °C (amorphous). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 163.9 (C), 163.8 (C), 160.6 (C), 160.3 (C), 136.5 (C), 128.8 (2 × CH), 127.3 (C), 113.8 (2 × CH), 108.0 (C), 99.3 (CH), 89.7 (CH), 55.4 (CH_3), 35.8 (CH_3), 32.1 (C), 30.4 (3 × CH_3), 27.6 (CH_2), 21.9 (CH_2), 21.9 (CH_2), 21.5 (CH_2). **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.24 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 5.58 (s, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 2.32–2.14 (m, 4H), 1.74–1.55 (m, 4H), 1.10 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{30}N_3O_3^+$ 396.2282; Found 396.2287.

1,3-Oxazin-4-one 4b. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 22 mg, 0.29 mmol) and aldimine **2c** (40 mg, 0.12 mmol) in 2.0 mL of anhydrous toluene, compound **4b** was obtained as a white solid (44 mg, 80%). **Rf** (EtOAc/ petroleum ether 1:7) = 0.12. **Mp** = 107 °C (amorphous). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 165.1 (C), 164.6 (C), 161.8 (C), 160.7 (C), 139.2 (C), 135.8 (C), 129.4 (2 × CH), 129.0 (2 × CH), 127.3 (CH), 126.0 (C), 124.2 (2 × CH), 113.4 (2 × CH), 107.9 (C), 103.3 (CH), 89.8 (CH), 55.4 (CH_3), 32.4 (C), 30.3 (3 × CH_3), 27.5 (CH_2), 22.0 (CH_2), 22.0 (CH_2), 21.6 (CH_2). **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.41–7.27 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.00 (s, 1H), 5.96 (s, 1H), 3.75 (s, 3H), 2.39–2.19 (m, 4H), 1.80–1.54 (m, 4H), 1.20 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{32}N_3O_3^+$ 458.2438; Found 458.2442.

1,3-Oxazin-4-one 4c. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 24.5 mg, 0.32 mmol) and aldimine **2d** (45 mg, 0.13 mmol) in 2.0 mL of anhydrous toluene, compound **4c** was obtained as a white solid (36 mg, 59%). **Rf** (EtOAc/petroleum ether 1:7) = 0.16. **Mp** = 150–151 °C (amorphous). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 164.7 (C), 164.4 (C), 162.0 (C), 139.0 (C), 135.8 (C), 135.5 (C), 132.6 (C), 129.2 (2 × CH), 129.1 (2 × CH), 128.3 (2 × CH), 127.4 (CH), 124.1 (2 × CH), 108.2 (C), 103.2 (CH), 89.2 (CH), 32.4 (C), 30.3 (3 × CH_3), 27.5 (CH_2), 21.9 (CH_2), 21.9 (CH_2), 21.5 (CH_2). **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.42–7.28 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.01 (s, 1H), 6.00 (s, 1H), 2.38–2.18 (m, 4H), 1.77–1.58 (m, 4H), 1.21 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}ClN_3O_2^+$ 462.1943; Found 462.1941.

1,3-Oxazin-4-one 4d. Following the general procedure at 180 °C with 2-diazocycloheptan-1,3-dione (2 × 56.5 mg, 0.74 mmol) and aldimine **2e** (90 mg, 0.31 mmol) in 2.0 mL of anhydrous toluene, compound **4d** was obtained as a white solid (90 mg, 70%). **Rf** (EtOAc/petroleum ether 1:2) = 0.20. **Mp** = 104–105 °C (amorphous). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 164.2 (C), 164.2 (C), 160.8 (C), 149.9 (C), 137.9 (C), 133.5 (C), 128.9 (2 × CH), 128.6 (2 × CH), 127.6 (CH), 127.1 (C), 125.4 (2 × CH), 114.1 (2 × CH), 107.8 (C), 100.0 (CH), 89.8 (CH), 55.4 (CH_3), 36.3 (CH_3), 27.7 (CH_2), 22.0 (CH_2), 22.0 (CH_2), 21.5 (CH_2). **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.62 (d, *J* = 8.7 Hz, 2H), 7.34–7.29 (m, 4H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.28 (s, 1H), 6.11 (s,

1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.38–2.16 (m, 4H), 1.80–1.65 (m, 4H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{26}N_3O_3^+$ 416.1969; Found 416.1969.

1,3-Oxazin-4-one 4e. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 19.5 mg, 0.26 mmol) and ketimine **2f** (30 mg, 0.11 mmol) in 2.0 mL of anhydrous toluene, compound **4e** was obtained as a white solid (35 mg, 80%). **Rf** (EtOAc/petroleum ether 1:10) = 0.27. **Mp** = 119 °C (amorphous). **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): 164.7 (C), 162.3 (C), 162.2 (C), 139.2 (C), 135.8 (C), 129.0 (2 × CH), 127.4 (CH), 124.3 (2 × CH), 106.9 (C), 102.5 (C), 102.1 (CH), 35.7 (CH_2), 35.0 (CH_2), 32.6 (C), 30.5 (3 × CH_3), 27.9 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.2 (CH_2), 22.1 (CH_2), 21.4 (CH_2). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.48 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 6.13 (s, 1H), 2.35–2.30 (m, 3H), 2.10–2.09 (m, 2H), 1.75–1.52 (m, 11H), 1.34 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{32}N_3O_2^+$ 406.2489; Found 406.2489.

1,3-Oxazin-4-one 4f. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 29.5 mg, 0.39 mmol) and ketimine **2g** (70 mg, 0.16 mmol) in 2.0 mL of anhydrous toluene, compound **4f** was obtained as a yellow solid (74 mg, 83%, dr = 1:1.6). **Rf** (EtOAc/petroleum ether 1:10) = 0.10. **$^{13}C\{^1H\}$** NMR (75 MHz, δ ppm/$CDCl_3$): major diastereomer: 171.0 (C), 165.0 (C), 162.2 (C), 162.0 (C), 142.7 (C), 139.2 (C), 135.0 (C), 134.1 (C), 131.8 (CH), 129.2 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 127.2 (CH), 125.6 (CH), 124.5 (CH), 123.6 (C), 123.2 (CH), 109.3 (CH), 106.9 (C), 102.2 (CH), 89.7 (C), 44.2 (CH_2), 32.4 (C), 30.2 (3 × CH_3), 27.5 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 21.3 (CH_2); minor diastereomer: 168.7 (C), 163.4 (C), 162.7 (C), 161.6 (C), 142.7 (C), 139.0 (C), 134.9 (C), 134.5 (C), 132.1 (CH), 129.0 (CH), 128.9 (CH), 128.9 (C), 127.9 (CH), 127.4 (CH), 127.3 (CH), 125.2 (CH), 124.4 (CH), 123.3 (CH), 110.0 (CH), 107.7 (C), 101.5 (CH), 88.8 (C), 44.0 (CH_2), 32.3 (C), 30.3 (3 × CH_3), 27.7 (CH_2), 22.0 (CH_2), 21.9 (CH_2), 21.2 (CH_2). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): major diastereomer: 7.43–7.24 (m, 10H), 7.12–7.07 (m, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 7.0 Hz, 1H), 5.94 (s, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.70 (d, *J* = 15.6 Hz, 1H), 2.48–2.38 (m, 2H), 2.28–2.11 (m, 2H), 1.84–1.72 (m, 4H), 1.07 (s, 9H); minor diastereomer: 7.54–7.52 (m, 2H), 7.43–7.24 (m, 8H), 7.12–7.07 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 4.20 (d, *J* = 15.6 Hz, 1H), 2.48–2.38 (m, 2H), 2.28–2.11 (m, 2H), 1.84–1.72 (m, 4H), 1.18 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{35}H_{35}N_4O_3^+$ 559.2704; Found 559.2707.

1,3-Oxazin-4-one 4g. Following the general procedure at 150 °C with 2-diazocycloheptan-1,3-dione (2 × 34.5 mg, 0.45 mmol) and ketimine **2h** (70 mg, 0.19 mmol) in 2.0 mL of anhydrous toluene, compound **4g** was obtained as a yellow solid (72 mg, 77%, dr = 1:1.6). **Rf** (EtOAc/petroleum ether 1:5) = 0.10. **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): major diastereomer: 169.1 (C), 163.0 (C), 162.6 (C), 160.2 (C), 142.6 (C), 134.5 (C), 133.6 (C), 132.2 (CH), 129.1 (CH), 128.0 (CH), 127.0 (CH), 126.2 (C), 124.4 (CH), 123.9 (CH), 110.5 (CH), 106.6 (C), 98.7 (CH), 89.5 (C), 44.4 (CH_2), 35.9 (CH_3), 32.1 (C), 30.4 (3 × CH_3), 27.7 (CH_2), 22.0 (CH_2), 22.0 (CH_2), 21.2 (CH_2); minor diastereomer: 170.7 (C), 163.2 (C), 162.1 (C), 160.6 (C), 143.0 (C), 134.9 (C), 134.6 (C), 131.9 (CH), 129.3 (CH), 128.2 (CH), 127.9 (CH), 124.6 (C), 124.5 (CH), 123.7 (CH), 109.8 (CH), 106.9 (C), 98.7 (CH), 89.3 (C), 44.3 (CH_2), 35.6 (CH_3), 32.0 (C), 30.2 (3 × CH_3), 27.5 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 21.2 (CH_2). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): major diastereomer: 7.62 (d, *J* = 7.2 Hz, 1H), 7.33–7.24 (m, 5H), 7.10–7.02 (m, 2H), 6.67–6.64 (m, 1H), 5.01 (s, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 3.75 (s, 3H), 2.42–2.17 (m, 4H), 1.84–1.56 (m, 4H), 1.06 (s, 9H); minor diastereomer: 7.33–7.24 (m, 4H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.10–7.02 (m, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.67–6.64 (m, 1H), 5.48 (s, 1H), 5.00 (d, *J* = 15.3

Hz, 1H), 4.63 (d, *J* = 15.3 Hz, 1H), 3.57 (s, 3H), 2.42–2.17 (m, 4H), 1.84–1.56 (m, 4H), 0.93 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{30}H_{33}N_4O_3^+$ 497.2547; Found 497.2536.

1,3-Oxazin-4-one 4h. Following the general procedure at 150 °C with 2-diazocyclooctan-1,3-dione (2 × 39 mg, 0.35 mmol) and aldimine **2c** (49 mg, 0.15 mmol) in 2.0 mL of anhydrous toluene, compound **4h** was obtained as a white solid (25 mg, 36%). **Rf** (EtOAc/petroleum ether 1:7) = 0.18. **Mp** = 115 °C (amorphous). **$^{13}C\{^1H\}$ NMR** (100 MHz, δ ppm/$CDCl_3$): 169.4 (C), 165.0 (C), 161.8 (C), 160.6 (C), 139.3 (C), 136.1 (C), 129.3 (2 × CH), 129.0 (2 × CH), 127.3 (CH), 126.3 (C), 124.2 (2 × CH), 113.5 (2 × CH), 112.2 (C), 103.1 (CH), 89.8 (CH), 55.5 (CH_3), 33.6 (CH_2), 32.4 (C), 31.6 (CH_2), 30.3 (3 × CH_3), 26.9 (CH_2), 24.8 (CH_2), 23.6 (CH_2). **^1H NMR** (400 MHz, δ ppm/$CDCl_3$): 7.40–7.28 (m, 5H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.98 (s, 1H), 5.97 (s, 1H), 3.76 (s, 3H), 2.53–2.30 (m, 4H), 1.74–1.69 (m, 2H), 1.60–1.46 (m, 4H), 1.20 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{34}N_3O_3^+$ 472.2595; Found 472.2598.

1,3-Oxazin-4-one 4i. Following the general procedure at 180 °C with 2-diazoacetylacetone (2 × 27 mg, 0.43 mmol) and aldimine **2c** (60 mg, 0.18 mmol) in 2.0 mL of anhydrous toluene, compound **4i** was obtained as a pale yellow solid (50 mg, 64%). **Rf** (EtOAc/petroleum ether 1:8) = 0.19. **Mp** = 60 °C (amorphous). **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): 165.5 (C), 162.4 (C), 161.8 (C), 160.6 (C), 139.2 (C), 135.8 (C), 129.3 (2 × CH), 129.0 (2 × CH), 127.3 (CH), 126.1 (C), 124.2 (2 × CH), 113.4 (2 × CH), 105.9 (C), 103.1 (CH), 89.5 (CH), 55.4 (CH_3), 32.4 (C), 30.3 (3 × CH_3), 17.5 (CH_3), 10.6 (CH_3). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.40–7.27 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 5.99 (s, 1H), 5.94 (s, 1H), 3.75 (s, 3H), 1.96 (s, 3H), 1.85 (s, 3H), 1.20 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{30}N_3O_3^+$ 432.2282; Found 432.2283.

1,3-Oxazin-4-one 4j. Following the general procedure at 180 °C with 2-diazoacetylacetone (2 × 32 mg, 0.51 mmol) and aldimine **2i** (80 mg, 0.21 mmol) in 2.0 mL of anhydrous toluene, compound **4j** was obtained as a white solid (49 mg, 49%). **Rf** (EtOAc/petroleum ether 1:5) = 0.11. **Mp** = 46 °C (amorphous). **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): 163.7 (C), 161.9 (C), 160.9 (C), 137.9 (C), 135.5 (C), 132.1 (2 × C, $^2J_{C\text{-}F}$ = 33.7 Hz), 127.7 (2 × CH, $^3J_{C\text{-}F}$ = 2.7 Hz), 123.7 (CH, $^3J_{C\text{-}F}$ = 3.6 Hz), 122.9 (2 × C, $^1J_{C\text{-}F}$ = 271.2 Hz), 106.9 (C), 99.4 (CH), 88.1 (CH), 35.5 (CH_3), 32.2 (C), 30.2 (3 × CH_3), 17.5 (CH_3), 10.5 (CH_3). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.84 (s, 1H), 7.82 (s, 2H), 6.34 (s, 1H), 5.66 (s, 1H), 3.56 (s, 3H), 2.07 (s, 3H), 1.86 (s, 3H), 1.11 (s, 9H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{24}F_6N_3O_2^+$ 476.1767; Found 476.1767.

1,3-Oxazin-4-one 4k. Following the general procedure at 180 °C with 2-diazoacetylacetone (2 × 26 mg, 0.41 mmol) and aldimine **2j** (75 mg, 0.20 mmol) in 2.0 mL of anhydrous toluene, compound **4k** was obtained as a white solid (59 mg, 62%). **Rf** (EtOAc/petroleum ether 1:4) = 0.25. **Mp** = 81 °C (amorphous). **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): 160.5 (C), 149.9 (C), 137.6 (C), 136.7 (C), 133.4 (C), 128.8 (2 × CH), 128.5 (2 × CH) , 128.4 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 127.6 (CH), 126.9 (C), 125.4 (2 × CH), 113.8 (2 × CH), 105.5 (C), 100.6 (CH), 89.1 (CH), 55.2 (CH), 53.5 (CH_2), 17.5 (CH_3), 10.4 (CH_3). **^1H NMR** (300 MHz, δ ppm/$CDCl_3$): 7.69–7.63 (m, 2H), 7.36–7.29 (m, 5H), 7.23 (m, 3H), 7.07 (d, 2H), 6.75 (d, 2H), 6.11 (s, 1H), 5.94 (s, 1H), 5.30 (d, *J* = 15.4 Hz, 1H), 5.21 (d, *J* = 15.4 Hz, 1H), 3.76 (s, 3H), 1.93 (s, 3H), 1.85 (s, 3H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{28}N_3O_3^+$ 466.2125; Found 466.2126.

Cyclodimer 5a. A solution of 2-diazocyclohexan-1,3-dione (70 mg, 0.51 mmol) in 2.5 mL anhydrous toluene was irradiated with microwaves at 160 °C for 5 minutes, cooled down to 55 °C by an air flow and concentrated to afford cyclodimer **5a** (57 mg, quant.) as a pale yellow oil. **Rf** (EtOAc/petroleum ether 3:2) = 0.68. **$^{13}C\{^1H\}$ NMR** (75 MHz, δ ppm/$CDCl_3$): 204.0, 184.4,

172.3, 166.5, 115.6, 72.0, 38.1, 32.1, 30.4, 25.7, 20.3, 18.8. **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 2.90–2.56 (m, 4H), 2.57–2.47 (m, 2H), 2.43 (m, 2H), 2.23–1.94 (m, 4H). **HRMS** (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}O_4^+$ 221.0808; Found 221.0812.

Cyclodimer 6a. A solution of 2-diazocyclohexan-1,3-dione (267 mg, 2.0 mmol) and *N,N*-dimethylallylamine (240 μL, 2.0 mmol) in 3.0 mL anhydrous toluene was irradiated with microwaves at 160 °C for 10 minutes, cooled down to 55 °C by an air flow and concentrated to afford cyclodimer **6a** (195 mg, 88%) as a brown solid. Recrystallization of this material from toluene afforded colorless prisms suitable for X-ray diffraction structural analysis (CCDC 1975653). **Rf** (EtOAc/petroleum ether 1:4) = 0.10. **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 168.8, 165.4, 164.3, 161.0, 111.5, 107.5, 32.7, 31.5, 26.5, 25.9, 21.5, 19.9. **^{1}H NMR** (300 MHz, δ ppm/$CDCl_3$): 2.81–2.73 (m, 2H), 2.74–2.62 (m, 4H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.19 (tt, *J* = 7.2, 7.3 Hz, 2H), 2.05 (tt, *J* = 7.3, 7.4 Hz, 2H). The structure of **6a** was resolved by X-ray diffraction analysis (CCDC 1975653).

Pyran-2-one 8e. A solution of 2-diazoacetylacetone (65 mg, 0,52 mmol) in 2.0 mL of anhydrous toluene was irradiated with microwaves at 180 °C for 3 minutes, cooled down to 55°C by an air flow and concentrated in vacuum to afford a crude sticky solid, probably containing the cyclodimer **5e** as analyzed from its crude ^{1}H NMR at 300 MHz in $CDCl_3$ showing predominantly four singlet resonances of equal area at 2.23, 2.18, 1.83 and 1.72 ppm (see spectrum in the Supporting Information). This material was dissolved in diethyl ether, and the slow evaporation of this solution over several days in a tubular vial open to air afforded monocrystalline needles, which were washed with petroleum ether to afford **8e** (11 mg, 30%). **Rf** (EtOAc/petroleum ether 1:2) = 0.15. **Mp** = 179 °C (recrystallized from diethyl ether). **^{13}C{^{1}H} NMR** (75 MHz, δ ppm/$CDCl_3$): 165.7, 164.3, 155.6, 106.4, 98.0, 77.2, 17.2, 9.8, 8.3. **^{1}H NMR** (400 MHz, δ ppm/$CDCl_3$): 2.22 (s, 1H), 1.98 (s, 1H), 1.96 (s, 1H). The structure of **8e** was resolved by X-ray diffraction analysis (CCDC 1985157).

SUPPORTING INFORMATION

Copies of NMR spectra for all new compounds, and full-details computational studies (PDF); raw NMR data for all new compounds (ZIP); crystallographic data for compounds **6a** and **8e** (CIF).

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